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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,583	05/03/2002	Audrey Goddard	10466/350	2698

20995 7590 12/28/2005

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EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 12/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,583	GODDARD ET AL.	
	Examiner	Art Unit	
	Jon M. Lockard	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/30/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. The amendment of 30 September 2005 has been entered in full. Claims 72-79 are amended and claims 80-81 have been cancelled.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 72-79 and 82-84 are under consideration in the instant application.

Inventorship

3. The petition under 37 CFR 1.48(b) filed 05 November 2004 has been reviewed and is granted. The inventorship in this nonprovisional application has been changed by the deletion of Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen, and Colin K. Watanabe.

Information Disclosure Statement

4. The supplemental information disclosure statement filed on 30 September 2005 has been considered.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 101 and 35 USC § 112, first paragraph

5. Claims 4-17 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation.

The basis for this rejection is set forth for claims 4-17 at pg 4-12 of the previous Office Action (29 June 2005).

6. Specifically, claims 4-17 are directed to an isolated polypeptide comprising (a) the amino acid sequence of the polypeptide of SEQ ID NO: 74, (b) the amino acid sequence of the polypeptide of SEQ ID NO: 74, lacking its associated signal peptide, (c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:74, (d) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:74, including its associated signal peptide, or (e) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203248. The claims are also directed to an isolated polypeptide having at least 95% and 99% amino acid sequence identity to (a) the amino acid sequence of the polypeptide of SEQ ID NO: 74, (b) the amino acid sequence of the polypeptide of SEQ ID NO: 74, lacking its associated signal peptide, (c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:74, (d) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:74, including its associated signal peptide, or (e) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203248; wherein said polypeptide is more highly expressed in normal stomach, lung, rectal, or skin tissue compared to stomach, lung, rectal or melanoma tumor, respectively, or wherein said polypeptide is encoded by a polynucleotide that is more highly expressed in normal stomach, lung, rectal, or skin tissue compared to stomach, lung, rectal or melanoma tumor, respectively, or wherein said polypeptide or a fragment thereof can be used to generate an antibody which can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:74

in stomach, lung, rectal, or skin tissue samples. The claims also recite a chimeric polypeptide comprising a polypeptide fused to a heterologous polypeptide.

7. Applicant's arguments (30 September 2005), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

8. It is noted that at pages 11-14 of the Response, Applicant cites pertinent case law reviewing the legal standard of utility and the Utility Examination Guidelines. The Examiner takes no issue with Applicant's general comments regarding the legal standard for utility.

9. The specification does not disclose any secondary or tertiary structural features of the PRO1335 polypeptide, nor does it disclose any additional information regarding PRO1335 such as subcellular location, timing of regulation during cellular differentiation, which hormones or transcription factors regulate PRO1335, and what physiological significance PRO1335 plays. Therefore, it is a totally new, uncharacterized polypeptide with no well-established utility.

10. The record shows that Applicant relies primarily upon the asserted utility disclosed in Example 18, namely, that the claimed antibodies are useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of having a tumor (see, for example, pg 18 of the response). However, this asserted utility is not substantial for the following reasons.

11. In Example 18, the specification discloses that PRO1335 tested positive in a differential tissue expression analysis to detect underexpression/overexpression of PRO polypeptide-encoding nucleic acids in cancerous tumors (pp. 140-142). Quantitative PCR was used to detect differences in levels of cDNAs in cDNA libraries made from cancerous and normal tissues. Example 18 discloses that PRO1335 cDNA levels are: (1) higher in normal stomach as compared to stomach tumor; (2) higher in normal lung as compared to lung tumor; (3) higher in normal

rectum as compared to rectum tumor; and (4) higher in normal skin as compared to melanoma tumor. However, there is no evidence regarding whether or not PRO1335 polypeptide levels are also increased in these type of tumor. Furthermore, there is no disclosure of how great a difference in cDNA levels was detected. While this disclosure may provide utility and enablement for PRO1335 DNA, it does not provide utility nor enablement for PRO1335 polypeptides or antibodies.

12. Applicants argue that if the gene is differentially expressed in cancer versus non-cancer tissue, then the encoded polypeptide and antibodies which bind it are useful in diagnostics. The Declarations of Grimaldi (second declaration) and Polakis discuss the likelihood that if the nucleic acid is differentially expressed in tumors, then the encoded polypeptide will also be. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. Applicants also assert that the references of

Alberts (previously submitted as Exhibits 2 and 3) and Lewin (previously submitted as Exhibit 4) support the statements of Grimaldi and Polakis.

13. Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. While the Examiner agrees with the teachings of Alberts and Lewin that initiation of transcription is the most common point for a cell to regulate the gene expression, it is not the only means of regulating gene expression. For example, Alberts (Exhibit 2) also teaches that there are a number of other controls that can act later in the pathway from RNA to protein to modulate the amount of protein that is made, including translational control mechanisms and mRNA degradation control mechanisms (See Exhibit 2 at pg 453). Applicants previously submitted Exhibit 5 (Meric et al., 2002) which states the following:

> The fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. [M]ost efforts have concentrated on identifying differences in gene expression at the level or mRNA, which can be attributable to either DNA amplification or to differences in transcription.

However, Meric et al. also goes on to state that gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability (See page 971, Introduction). Meric et al. also teaches that there are a number of translation alterations encountered in cancer, including variations in the mRNA sequence as a result of mutations, alternate splicing and transcription start sites, alternate polyadenylation sites, and alterations in the components of the translation machinery (See pages 973-974). While Zhigang et al. (previously submitted as Exhibit 4) provides an example of a high degree of correlation between protein and mRNA expression of a specific antigen, the art also teaches that, in organisms ranging from yeast to human, changes in mRNA levels are not predictive of changes in the encoded polypeptide levels, especially in cancerous cells. For example, Hu et al. (2003, Journal

of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, **most** are attributable to disease-independent differences between the samples (2003, Nature Biotechnology 21:976-977). Similarly, Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. also disclose that the mRNA/protein correlation coefficient varied among proteins with multiple isoforms, indicating potentially separate isoform-specific mechanisms for the regulation of protein abundance. In this study using a quantitative analysis of mRNA and protein expression within the same lung adenocarcinomas, it is disclosed that only a minority subset of the proteins exhibited a significant positive correlation with mRNA abundance. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples"

(pp. 311-312). Lichtinghagen et al. (2002, European Urology. 42 :398-406) show a similar lack of correlation in matrix metalloproteinases (MMPs 2 and 9 and the tissue inhibitor of metalloproteinases 1 (TIMP-1) in human prostate cancer. After measuring differential expression at both the mRNA and protein level of the genes, they concluded that [C]omparison of mRNA and protein expression of MMP-2, MMp-9, and TIMP-1, respectively, did not show any significant relationships illustrating the necessity to study these components at both molecular levels" (See abstract, pg 398).

14. The art also shows that transcript levels do not necessarily correlate with protein levels in normal tissues. See Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances which varied more than 50-fold. Haynes et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Gygi et al. (1999, Mol. Cell. Biol. 19:1720-1730) conducted a similar study with over 150 proteins in yeast. They concluded that "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient" (Abstract). Lian et al. (2001, Blood 98:513-524) show a

similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract).

15. As supported by the studies cited above, the state of the art is such that polypeptide levels cannot be accurately predicted from mRNA levels. Madoz-Gurpide et al. (Adv Exp Med Biol 532: 51-58, 2003) even indicate that "[f]or most of the published studies it is unclear how well RNA levels reported correlate with protein levels. A lack of correlation may imply that the predictive property of the gene(s) is independent of gene function" (pg 53, 1st full paragraph). Furthermore, Celis et al. (FEBS Lett 480 : 2-16, 2000) state that a complementary technology to DNA microarrays for monitoring gene expression is provided by proteomics (pg 6, last paragraph in col 1). However, the specification of the instant application has only disclosed that the PRO1335 polynucleotide is slightly overexpressed (about 2-fold) in breast, colon, and lung tumors. The specification does not indicate that the PRO1335 polypeptide has been overexpressed in the breast, colon, and lung tumor samples tested. Celis et al. emphasize that proteins are frequently the functional molecules and, therefore, the most likely to reflect differences in gene expression (pg 6, bottom of col 1). Celis et al. continue to explain that "[g]enes may be present, they may be mutated, but they are not necessarily transcribed. Some messengers are transcribed but not translated, and the number of mRNA copies does not necessarily reflect the number of functional protein molecules" (pg 6, col 2). Madoz-Gurpide et

al. indicate that there is a need to utilize protein microarray strategies to address the many different features of proteins, including the determination of protein levels in biological samples (pg 53, 2nd full paragraph). There is also intense interest in the scientific field in applying proteomics to disease marker identification and such approaches include comparative analysis of protein expression in normal and cancer tissues to identify aberrantly expressed proteins that may represent novel markers (Madoz-Gurpide et al., pg 54, 2nd full paragraph).

16. As supported by the studies cited above, the state of the art is such that polypeptide levels cannot be accurately predicted from mRNA levels, and the specification of the instant application has not disclosed that the PRO1335 polypeptide is either overexpressed or underexpressed to the extent that it could be use as a diagnostic marker for any cancer.

17. Given the asserted decrease in PRO1335 mRNA expression and the evidence provided by the current literature, one skilled in the art would not consider it, more likely than not, that a small increase in expression (no quantitative data provided) would correlate with significantly increased polypeptide levels. In the absence of information regarding whether or not PRO1335 protein levels are also different between specific cancerous and normal tissues, the proposed use of the PRO1335 polypeptides as diagnostic markers and therapeutic targets are simply starting points for further research. Further research needs to be done to determine whether the small increase in PRO1335 mRNA expression supports a role for the encoded polypeptide as a diagnostic marker in the cancerous tissue, such that the claimed polypeptide could be used as a diagnostic target. Such further research requirements make it clear that the asserted utility is not

yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,
> "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

18. Accordingly, the specification's assertion that the PRO1335 polypeptides and antibodies which bind them have utility in the fields of cancer diagnostics and cancer therapeutics is not substantial.

19. Regarding Hu et al. (cited by Examiner in the previous Office Action), Applicant indicates at pg 20-21 of the response that among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease. Applicant argues that Hu et al. does not conclusively show that it is more likely than not that the gene amplification does not result in increased expression at the mRNA and polypeptide levels. Applicant contends that since Hu et al. only studies the statistical analysis of microarray data and not the gene amplification data, their findings would not be directly applicable to the gene amplification data. Applicant also states that Hu et al. manipulated various aspects of the input data.

20. Applicant's arguments have been fully considered but are not found to be persuasive.

The asserted utility for the claimed polypeptides is based on a sequence of presumptions. First, it is presumed that gene amplification predicts increased mRNA production. Second, it is presumed that increased mRNA production leads to increased protein production. Hu et al. is directly on point by showing that the second presumption is incorrect when designating proteins as diagnostic markers for cancer. Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease. The instant specification does not disclose that PRO1335 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, based on Hu et al., the skilled artisan would not reasonably expect that PRO1335 protein can be used as a cancer diagnostic. Regarding Applicant's criticism of Hu et al.'s statistical analysis, Applicant is holding Hu et al. to a higher standard than their own specification, which does not provide proper statistical analysis such as reproducibility, standard error rates, etc. Regarding Applicant's criticism of Hu et al. as being limited to a specific type of breast tumor, Hu et al. is cited as one of several pieces of evidence that gene amplification in a tumor does not correlate with mRNA overproduction or protein overproduction. When viewed with the evidence of record as a whole, there is no correlation between gene amplification, mRNA levels and protein levels. In view of the totality of the evidence, including the declarations submitted under 37 CFR 1.132 and the

publications of record, the instant utility rejection is appropriate.

21. At pages 19-20 of the Response of 05 October 2005, Applicant contends that the Haynes data (cited by Examiner in previous Office Action and above) confirm that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Applicant also points out that Haynes is not relevant to the current application because Haynes was studying yeast cells and not human cells. Applicant argues that Haynes did not compare mRNA expression levels and protein levels in the same yeast cells and thus the analysis by Haynes is not applicable to the present application.

32. Applicant's arguments have been fully considered but are not found to be persuasive. This has been fully considered but is not found to be persuasive because Haynes et al. clearly state "[p]rotein expression levels are not predictable from the mRNA expression levels" (pg 1863, top of left column) and "only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (pg 1870, under concluding remarks). Feroze-Merzoug et al. (Cancer and Metastasis Rev 20: 165-171, 2001) even disclose that "[t]he lack of correlation between mRNA and corresponding protein is evident even in low eukaryotic cells such as yeast. Therefore, it will be necessary to profile both mRNA and protein for a complete picture of how cells are altered during malignant transformation" (pg 168, col 1). Clearly, Haynes et al. and Feroze-Merzoug et al. indicate that mRNA levels do not predict protein levels.

23. At pg 21-23 of the Response, Applicant further asserts that the analysis of Chen et al. is not applicable to the instant application. Applicant indicates that the proteins selected for study by Chen et al. were those detectable by staining on 2D gels. Applicant states that Chen et al. are likely to have excluded many of the proteins most likely to be significant as cancer markers. Applicant also argues that Chen et al. does not account for different expression in different tissues or different stages of cancer. Applicant indicates that no attempt was made to compare expression levels in normal versus tumor samples and therefore, does not address the issue of whether increased mRNA levels in the tumor samples taken together as one group, as compared to the normal samples as a group, correlated with increased protein levels in tumorous versus normal tissue. Applicant concludes that in the Chen reference, even if the analysis presented is correct, a review of the correlation coefficient data presented in Chen et al. indicates that it is more likely than not that increased mRNA expression correlates with increased protein expression.

24. Applicant's arguments have been fully considered but are not found to be persuasive. Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and polypeptide expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). The instant specification does not provide additional information regarding whether or not PRO1335 polypeptide is more highly expressed

in normal stomach, lung, rectal, and skin tissue as compared to stomach, lung, rectal, and melanoma tumor, and thus the skilled artisan would need to perform additional experiments to reasonably confirm such. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial.

25. Applicant asserts that the Patent Office has failed to meet its initial burden of proof that Applicant's claims of utility are not substantial or credible. Applicant contends that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited references and application of an improper, heightened legal standard. Applicant states that the art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level.

26. Applicant's arguments have been fully considered but are not found to be persuasive. The truth, or credibility, of the assertion of utility has not been questioned. Rather, the rejection sets forth that the assertion of utility is not substantial. The preponderance of evidence supports this position. See Chen et al. (who found only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples), Hu et al. (who reviewed 2286 genes reported in the literature to be associated with breast cancer), Haynes et al., Lichtinghagen et al., Feroze-Merzoug et al., Madoz-Gurpide et al., and Celis et al. These references, taken into consideration with the disclosure, indicate to the skilled artisan that it is more likely than not that PRO1335 polypeptide is not useful as a cancer diagnostic agent.

27. In conclusion, the PRO1335 polypeptide instant application (SEQ ID NO:74) and the antibodies which bind to the PRO1335 polypeptide are not supported by either a specific and substantial ("real-world") asserted utility or a well-established utility. The polypeptide and antibody do not have a substantial utility because basic research is required to study the properties and activity of the polypeptide of SEQ ID NO:74. Until some actual and specific significance can be attributed to the protein identified in the specification as PRO1335, the instant invention is incomplete. In the absence of knowledge of the biological significance of this protein, there is no immediately obvious patentable use for it. Since the instant specification does not disclose a "real world" use for PRO1335 then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. § 101 as being useful.

35 U.S.C. § 112, first paragraph (Enablement)

28. Claims 4-17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The basis for this rejection is set forth for claims 4-17 at pg 12 of the previous Office Action (29 June 2005).

29. Applicant states that a specific and substantial asserted utility, has been described above. Specifically, since Applicant has not provided evidence to demonstrate that the PRO1335 polypeptide has a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. It is noted that the instant

specification is required to teach one skilled in the art how to make and use the claimed polypeptide.

30. However, even if the claimed invention is eventually deemed to have a credible, specific and substantial asserted utility or a well established utility, claims 4-5 and 12-17 would remain rejected under 35 U.S.C. § 112, first paragraph.

31. Applicant's arguments (30 September 2005), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

32. Regarding the recitation of variants and fragments in claims 4-5 and 12-17 at page 31 of the response of 30 September 2005, Applicant states that the pending claims are related to polypeptides having at least 95% or 99% amino acid sequence identity to several polypeptides related to SEQ ID NO:74, and which satisfy the limitation "wherein said isolated polypeptide is more highly expressed in normal stomach, lung, rectal, or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively, or "wherein said polypeptide is encoded by a polynucleotide that is more highly expressed in normal stomach, lung, rectal, or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively", or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:74 in stomach, lung, rectal, or skin tissue samples." Applicant asserts that since the claimed genus is characterized by a combination of structural and functional features, any person of skill would know how to make and use the invention without undue experimentation based on the general knowledge in the art at the time the invention was made. At page 31 of the Response, Applicant also argues that the specification teaches how to determine if the claimed polypeptides or encoding nucleic acids are differentially

expressed in stomach, lung, rectal, or skin tumor samples as compared to their normal tissues counterparts; how to make antibodies to the PRO1335 polypeptide of SEQ ID NO:74; and given the high amino acid sequence homology of the claimed variant polypeptides, one of skill in the art would know how to make antibodies to SEQ ID NO:74 from the claimed variant polypeptides.

33. Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, as discussed in the previous Office Action, certain positions in the polypeptide sequence are critical to the protein's structure/function relationship, e.g., such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. A large quantity of experimentation would be required by the skilled artisan to generate the infinite number of derivatives recited in the claims and screen the same for activity. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. No such variants were made or shown to have activity. Only the PRO1335 polypeptide of SEQ ID NO:100 is disclosed. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427

F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The recitation of the phrases "wherein said polypeptide is encoded by a polynucleotide that is more highly expressed in normal stomach, lung, rectal, or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively", or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:74 in stomach, lung, rectal, or skin tissue samples" in the claims is not adequate to describe the PRO1335 polypeptide or all possible variants that have at least 95% and 99% sequence identity to the PRO1335 polypeptide, since there was no reduction to practice to support the amended claims. Furthermore, while one could ready use variants of the polypeptide of SEQ ID NO:74 to make antibodies, one skilled in the art would expect that the use of such variant sequences to make antibodies would produce antibodies that lose their specificity as probes for the target or reference sequence.

34. Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 U.S.C. § 112, first paragraph (written description)

35. Claims 4-5 and 12-17 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth for claims 4-5 and 12-17 at pg 14-17 of the previous Office Action (29 June 2005).

36. Applicant's arguments (30 September 2005), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

37. It is noted that at pages 32 of the Response, Applicant cites pertinent case law reviewing the legal standard of written description. The Examiner takes no issue with Applicant's general comments regarding the legal standard for written description.

38. Applicants argue at pages 33-34 of the response (filed 30 September 2005) that based on the high percentage of sequence identity, there is no substantial variation within the species which fall within the scope of the amended claims, which require at least 95% or 99% amino acid sequence identity to the disclosed sequences related to SEQ ID NO:74. Applicants further argue that the pending claims are analogous to the claims discussed in Example 14 of the written description training materials. Applicants argue at pg 34-35 of the response that the facts in *In re Wallach* (71 USPQ2d 1939, 1942 Fed. Cir 2004) are very similar to the instant case and state, for example, if an applicant disclosed on amino acid sequence, it would be unnecessary to provide an explicit disclosure of nucleic acid sequence that encoded the amino acid sequences. Lastly, Applicants argue that the specification discloses how to test to determine if the polypeptide or

encoding nucleic acid is differentially expressed in stomach, lung, rectal or skin tumors, and how to make antibodies which specifically detect the polypeptide of SEQ ID NO:74 in stomach, lung, rectal, or skin tissue samples.

39. Applicant's arguments have been taken into consideration and are not found persuasive for the following reasons.

40. Regarding Applicants citation of *In re Wallach*, While the Examiner agrees that it is unnecessary to provide an explicit disclosure of the entire genus of nucleic acid sequence that encode a single amino acid sequence, it is noted that the instant claims are not drawn to a genus of nucleic acids that encode a single amino acid. The instant claims are drawn very broadly to a genus of polypeptide molecules that have at least 95% or 99% amino acid sequence identity to several polypeptides related to SEQ ID NO:74, and which satisfy the limitation "wherein said isolated polypeptide is more highly expressed in normal stomach, lung, rectal, or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively, or "wherein said polypeptide is encoded by a polynucleotide that is more highly expressed in normal stomach, lung, rectal, or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively", or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:74 in stomach, lung, rectal, or skin tissue samples". Applicant has not described or shown possession of all polypeptides that share 95% and 99% sequence identity to SEQ ID NO: 74, that still retain the function of SEQ ID NO: 74. Nor has Applicant described a representative number of species that share 95% and 99% sequence identity to SEQ ID NO: 74, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 74. Since one skilled in the art could not

envision the detailed chemical structure of all or a significant number of encompassed PRO1335 polypeptides, one skilled in the art would not know how to make or use them. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making and screening the same for activity or expression patterns/levels. The claimed product itself is required. Furthermore, recitation of the phrases "wherein said polypeptide is encoded by a polynucleotide that is more highly expressed in normal stomach, lung, rectal, or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively", or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:74 in stomach, lung, rectal, or skin tissue samples" in the claims is not adequate to describe the PRO1335 polypeptide or all possible variants that have at least 95% and 99% sequence identity to the PRO1335 polypeptide, since there was no reduction to practice to support the amended claims. Lastly, recitation of "wherein said polypeptide is more highly expressed in normal stomach, lung, rectal or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively" or "wherein said polypeptide is encoded by a polynucleotide that is more highly expressed in normal stomach, lung, rectal, or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively", or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:74 in stomach, lung, rectal, or skin tissue samples" in the claims is not a functional limitation contrary to the Applicants assertion nor does it provide adequate written description of all the possible variants that have at least 95% and 99% sequence identity to SEQ ID NO:74 that are also "more highly expressed" in normal stomach, lung, rectal or skin tissue compared to

stomach, lung, rectal, or melanoma tumor, respectively. Furthermore, the broad-brush discussion of making and screening for variants disclosed in the specification does not constitute a disclosure of a representative number of members. No such variants were made or shown to have an activity. The specification's general discussion of making and screening for variants constitutes and invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed variants. Additionally, the fact pattern of the instant application is not analogous to Example 14 in the Revised Interim Written Description Guidelines. In Example 14 of the Guidelines, the protein and variants have a specific activity disclosed in the specification. However, regarding PRO1335 polypeptides of the instant invention, the specification does not teach any significance or functional characteristics of the PRO1335 polypeptide. Applicants made no variant polypeptides nor have they shown that any PRO1335 polypeptide is more highly expressed in normal stomach, lung, rectal or skin tissue compared to stomach, lung, rectal or melanoma tumor respectively, and as recited in the current Written Description Guidelines, Applicants must have invented the subject matter that is claimed and must be in "possession" of the claimed genus (Federal Register, 2001, Vol. 66, No. 4, pages 1099-1111, esp. page 1104, 3rd column).

41. Furthermore, the broad brush discussion of making and screening for variants in the instant specification does not constitute a disclosure of a representative number of members. No such variants were made or shown to have activity. Only the PRO1335 polypeptide of SEQ ID NO:74 is disclosed. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such does not constitute an adequate

written description for the claimed variants. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factors present in the claims are a partial structure in the form of a recitation of percent identity and a requirement that the protein or the encoding nucleic acids are more highly expressed in normal stomach, lung, rectal or skin tissue as compared to stomach, lung, rectal or melanoma tumor respectively, or that the polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:74 in stomach, lung, rectal, or skin tissue samples. There is no identification of any particular portion of the structure that must be conserved in order to conserve the required function. Additionally, there is the issue of whether or not the single disclosed embodiment is actually differentially expressed in stomach, lung, rectal, and melanoma tumors (see rejection under 35 U.S.C. §§ 101 and 112, first paragraph, above). Clearly, such does not constitute disclosure of a representative number of examples of, nor adequate written description for, the claimed genus.

42. Therefore, only the polypeptide set forth as SEQ ID NO:74, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion

43. No claims are allowable.

44. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard, Ph.D.** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback**, can be reached on **(571) 272-0961**.

The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

JML
December 20, 2005